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REDAKSIONEEL · EDITORIAL

VERSTEURING VAN PIGMENTMETABOLISME IN GEVALLE VAN ADDISON SE SIEKTE

Die skrywers* verstrek eers 'n oorsig van die hedendaagse kennis van die fisiologie van pigmentmetabolisme en die afwykings wat aangetref word in gevalle waar daar 'n adrenokortikale gebrek is, en beskryf dan een van hul eie gevalle van Addison se siekte wat veral merkwaardig is omdat dit 'n voorbeeld verstrek van verspreide huidmelanose wat in byna algehele depigmentasie verander het.

Die geval was dié van 'n 59-jarige man wat meer as 25 jaar lank aan 'n adrenokortikale gebrek van 'n tuberkuleuse oorsprong gely het. Ongeveer 15 jaar lank was melanose die enigste simptoom. Eers in 1949 het duidelike tekens van Addison se siekte hul verskyning gemaak. Op daardie stadium het hy vitiligoagtige depigmentasiekolle begin toon wat geleidelik toegeneem het totdat die vel van sy romp en ekstremiteite teen 1953 volkome gedepigmenteer was. Die oorsaak van die verlies van pigment was 'n sekondêre gebrek van die voorste harsingslymklier, vergesel van uitputting van die aktiwiteit van ACTH en van die hormone wat die melanosiete stimuleer. Geen tekens van skildklier- of geslagskliergebreke is waargeneem nie. Die patogenese van die depigmentasie was nie duidelik nie; daar is egter veronderstel dat die groot dosisse vitamien C wat die man ontvang het, 'n invloed uitgeoefen het.

*Ziegenspeck, D. en Nitschke, U. (1960): Dtsch. Med. Wschr., **85**, 110.

DISTURBANCE OF PIGMENT METABOLISM IN ADDISON'S DISEASE

After reviewing present-day knowledge of the physiology of pigment metabolism and the deviations encountered in the presence of adrenocortical insufficiency, the authors* described one of their own cases of Addison's disease which is particularly noteworthy because it provides an example of diffuse cutaneous melanosis turning into almost complete depigmentation.

The case was that of a 59-year-old man who had had adrenocortical insufficiency of tuberculous origin for more than 25 years. For some 15 years melanosis was the only symptom. Not until 1949 did clearcut signs of Addison's disease appear. At that time he had patches of vitiligo-like depigmentation which gradually increased until, by 1953, the skin on his trunk and extremities was completely depigmented. The cause of the loss of pigment was secondary insufficiency of the anterior pituitary, accompanied by exhaustion of the activity of ACTH and of the hormone that stimulates the melanocytes. No signs of thyroid or gonadal deficiency were observed The pathogenesis of the depigmentation was obscure; it was supposed that the large doses of vitamin C which the man had received exerted some influence.

This clinical picture is not to be confused with a ' white ' (i.e. normally pigmented) case

* Ziegenspeck, D. and Nitschke, U. (1960): Dtsch. Med. Wschr., **85**, 110.

Hierdie kliniese beeld moet nie verwar word met 'n 'wit' (d.w.s. normaal gepigmenteerde) geval van Addision se siekte wat te wyte is aan 'n konstitusionele gebrek aan pigment en aan 'n onvermoë om die produksie van melanien te verhoog nie; in sulke gevalle is al wat ontbreek net één simptoom van Addison se siekte.

AANTEKENING I.V.M. CHOLESTEROL

Geen kwantitatiewe of kwalitatiewe verskille in die serumcholesterolpeil is aangetref by babetjies wat met 'n bottel en babetjies wat aan die bors gevoed is nie, hoewel die konsentrasies van onversadigde vetsure in moedersmelk en koeimelk heelwat van mekaar verskil.

[Gotlieb, A., Abramov, M., Schwarz, M. en Pessach, I. (1960): Harefuah (Israel), **58**, 43.]

of Addison's disease due to constitutional lack of pigment and inability to increase the production of melanin; in such instances, all that is missing is just one symptom of Addison s disease.

FOOTNOTE ON CHOLESTEROL

No quantitative or qualitative differences in the serum cholesterol level were found between bottle-fed and breast-fed infants, although the concentrations of unsaturated fatty acids in mother's milk and cow's milk differ considerably from each other.

[Gotlieb, A., Abramov, M., Schwartz, M. and Pessach, I. (1960): Harefuah (Israel), **58**, 43.]

ABSTRACTS

ECG PATTERNS AT HIGH ALTITUDES

Chronic hypoxia at high altitudes provokes certain cardiac changes in normal human beings. Measurement of teleroentgenograms, e.g. showed that the diameter of the heart and the heart shadow become enlarged. The right heart in particular is affected. The possibility of racial differences may be excluded. The changes are found only in subjects who have spent a sufficiently long time at high altitudes.

Electrocardiographic studies of normal subjects in Morococha (Peru), at an altitude of 4,545 metres (14,910 ft.), yielded the following results:

Only in 17.5% of cases was the ECG normal. In 19.2% the characteristic signs of right ventricular hypertrophy were clearly apparent, and in 32.5% there was a strong suspicion of this abnormality; 30.8% of the cases had complete or incomplete right bundle branch block. It is supposed that right ventricular hypertrophy is connected with the pulmonary hypertension which is frequently encountered at high altitudes.

It may be regarded as characteristic of the ECG at high altitudes that negative deflections in the QRS complex, which are to be attributed to an anomaly in the position of the heart, should predominate in both normal and precordial leads. The adaptation of the respiration to high altitudes, combined with expansion of the thorax and increased ventilation per minute, causes the longitudinal axis of the heart to turn in a clockwise direction and the apex to move to the rear.

[Rotta, A. and López, A. (1959): Circulation, **19**, 719].

THE AUTONOMIC NERVOUS SYSTEM IN MOUNTAIN CLIMATES

Halhuber deals with the various influences of high altitudes on normal and diseased subjects. In one section an account is given of the effects of a mountain railway journey on subjects with a normal cardiovascular system. The reactions to a brief change in altitude can be described as follows:

Immediately upon arrival at the high altitude the circulation shows a vagotonia which is expressed subjectively chiefly as fatigue and lasts a few hours. Then follows a second phase of circulatory adjustment which is termed altitude amphotonia. The pulse rate rises, pulse pressure and minute volume increase, the tone of the large arteries is enhanced, and the pulse wave velocity is accelerated. Respiration deepens, the sensitivity of all the sense organs is increased, muscle tone is enhanced, and the blood adrenaline level rises. The amount of circulating blood and the erythrocyte count increase as the deposits are emptied.

Altitude amphotonia makes itself subjectively felt in the form of increased excitability; it is reflected in slight finger tremor, poor sleep and enhanced response to caffeine and sympathomimetic agents. This second phase lasts 1–2 days at an altitude of 2,000 metres (6,560 ft.), and about 5 days at an altitude of 3,000 metres (9,840 ft.).

The 'change in climate' brought about by mountain railway journeys constitutes a specific form of therapy based on high altitude stimulation. This 'shock attack' on the autonomic nervous system provides a salutary stimulus, as a result of which the organism's regulatory processes are stabilized anew.

[Halhuber, M. J. (1959): Münch. Med. Wschr., **101**, 1118].

FIBRIN AND VASCULAR DISEASE

In the blood there are numerous proteolytic and antiproteolytic factors which are normally in perfect equilibrium. This equilibrium can be upset by fibrin which binds proteolytic factors (plasmokinase, plasmin) to its surface. Processes of this type presumably play a part in the development and progress of certain vascular diseases.

[Yatzidis, H. (1959): Rev. Franç. Études Clin. Biol., **4**, 383].

A SURVEY OF ANAESTHESIA IN GREAT BRITAIN

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During a 6-months' stay in Great Britain I visited various hospitals in order to observe the practice of anaesthesia. This report describes shortly different techniques observed and also discusses some of them.

Guy's Hospital. Here I spent some time watching anaesthesia for cardiac surgery. In most of the cases the by-pass pump was used in conjunction with hypothermia. The heat reactor is connected to the pump; the cooling is done by the veno-venous method, i.e. by inserting cannulae into the superior and inferior venae cavae. The advantage of this method is that the surgeon can have the cooling done to the required temperature in a matter of minutes. As soon as hypothermia is no longer necessary, re-warming can be done very rapidly. The cases which I saw were cooled down to between 25–30° C.

The heart-lung machine (the disc oxygenator type) and the cooling apparatus were both built at Guy's Hospital. The work was impressive and was carried out with the minimum of personnel.

Great Ormond Street Children's Hospital. Here I had an excellent opportunity of watching experts in paediatric anaesthesia. The efficient assistance given to the anaesthetist during the induction stage was impressive. The anaesthetic technician (who prepares the equipment for each case and assists the anaesthetist with the anaesthetic) is usually a man with years of experience in this particular branch of anaesthesia. He knows exactly what is needed for each case and how to assist with whatever technique is being used. In most of the abdominal cases and, naturally, in the open thoracotomy cases, controlled respiration is used. For children up to about 4 years the Ayres T-piece and bag and hyperventilation method is used; after that age the Waters to-and-fro carbon dioxide absorption technique is practised. At this hospital a method of premedication favoured is to give, one hour before the operation, an intramuscular injection of Phenergan 50 mg., Largactil 50 mg. and Pethidine 200 mg. This makes up an 8 c.c. mixture. Of this 1 c.c. per 20 lb. is given. The patient is usually asleep or well sedated by the time the induction is started (usually with Cyclopropane) and then the relaxant is given intravenously, irrespective of the age of the child. In babies the site of injection is usually on the back of the hand or the scalp veins, depending on the size of the veins. A Rigby needle with a length of polythene, at the end of which is a rubber diaphragm, is generally used. The anaesthetist can then give any further intravenous injections from a position out of the way of the surgical team.

During the first few weeks of a child's life most of the cases are intubated without an anaesthetic; the relaxant is then given, followed by the rest of the anaesthetic. Dr. Hawksley favours laryngoscopy of the neonates whilst they are awake. As soon as the glottis is visualized, an assistant gives the required dose of Succinylcholine intravenously and the patient is then immediately intubated and inflated. The rationale for this technique is that it is impossible properly to inflate the lungs in a paralysed neonate by the use of a face mask. In the first place, it is difficult at that age to get a face mask to fit tightly and, in any case, the stomach would be blown up in the process. Distended stomach as a result of inflation can present quite a problem in small babies, especially in abdominal operations. Dr. Sheila Anderson, as a routine, passes a stomach tube in these cases at the beginning of the operation, and again at the end, to deflate the stomach.

One of the problems in neonate anaesthesia is that a marked degree of hypothermia may occur during a prolonged anaesthetic entailing controlled respiration with a high flow of gases and the T-piece method. The heat control centre is poorly developed at this age. If the muscles are paralysed and hyperventilation is carried out with cold gases, the temperature of the child can drop appreciably.

Illustrative Case: A case of imperforate anus in a child of 5 days old was operated on, using the above method. Intermittent doses of Succinylcholine were given intravenously for the duration of the operation, which took about 3 hours. At the end of the operation the child remained apnoeic in spite of the usual methods of resuscitation. It was then noticed that the child was very cold and, on taking the oral temperature, this was found to be 87°F. The baby was then immersed in a warm bath at a temperature of 40°C. and massaged. At the end of 20 minutes the temperature rose to 93°F. and the child started breathing.

It is worth remembering that Jackson Rees warns against this complication in neonates. He points out that these small babies should always be covered by wrapping cotton wool around the limbs during anaesthesia, to limit drop in temperature.

Middlesex Hospital. Hewer went to a great deal of trouble to demonstrate the various techniques he used as well as the electrophysical aids in which he is interested. He is working on an electrical pulse and blood pressure recorder.

Halothane is used extensively in this hospital. It was interesting that in a case where this technique was used with a non-return valve and spontaneous breathing, the tidal respiration was only 200 c.c. and the minute volume 4,480 c.c. Respiration was not assisted! Hewer says that during Halothane anaesthesia the metabolism is reduced and that the above minute volume is quite satisfactory.

The question of diminished minute volume in spontaneous respiration in anaesthesia will be referred to later.

At this same hospital Sellick (who was doing a cardiac list during my visit) intubated the cases with the use of a mixed relaxant consisting of 30 mg. Tubarine and 100 mg. Succinylcholine in the same syringe. The advantage of this method is that the patient is well relaxed for the intubation due to the depolarizer. When this wears off the non-depolarizing effect is present and there is no straining on the tube. If there is apnoea at the end of the operation due to relaxant, it can be reversed by the use of neostigmine, the argument being that if it is due to the action of the depolarizer it will be due to the dual blocking action of this drug. This technique is only used in long cases.

A case of ventricular septal defect was operated on by the use of a heart-lung machine of the screening type, the by-pass being used for 45 minutes. Hypothermia by surface cooling was used on a rather fat woman for an atrial septal defect. She was placed in a cold bath for 1½ hours before the temperature dropped to 32° C. Pummelling and kneading of muscles to assist the speed of cooling was also employed. When a temperature of 32° C. was reached, the operation commenced. The patient was then placed on a warm mattress and warm covers applied. The repair of the heart took 10 minutes. At the end of the operation the patient was submerged in a warm bath until her temperature reached 35° C., when she was returned to the ward. The blood pressure readings were taken in the bath by means of an oscillometer.

St. Thomas' Hospital. Churchill Davidson used a mixture of 2.5% Pentothal and 60 mg. Flaxedil in a 10 c.c. syringe, as a routine for cases of varicose veins operations for which intermittent doses of this mixture are given. He judged his dosage according to the requirements of the operation, the aim being to cause paralysis of the legs, without affecting the diaphragm and the intercostals. A mask and an airway are used for giving nitrous oxide and oxygen. The respiration is not affected. A non-return valve is used and he does not intubate even for cases in a prone position. It must be emphasized that he utilizes this technique only for cases of stripping of varicose veins, orthopaedic cases and suitable plastic operations. He claims that his patients have a very comfortable recovery and never complain of nausea or vomiting.

Interesting electromyograph experiments were also demonstrated showing that the spike potential is not affected by the depolarizers but very definitely by the non-depolarizing relaxants.

Royal College of Surgeons. Extremely interesting research work is being done by Professor Woolmer, Dr. Nunn and Dr. Graham, a physiologist. They are interested in the effect of CO_2 on the dog. At my visit, 40 dogs had been used in these experiments. Their findings are, briefly, that when CO_2 is given in concentrations of up to 20% with 15% Cyclopropane anaesthesia, the minute volume increases and then remains stationary. If the Cyclopropane is then turned off, the minute volume again steeply increases until the CO_2 concentration reaches a level of over 30% and then diminishes until the CO_2 climbs to 45%, when the dog becomes apnoeic. If ventilation is persisted with 45% $CO_2 + O_2$ for 20 minutes, the dog starts breathing again. During the Cyclopropane anaesthesia and with a CO_2 concentration as high as 20%, no cardiac arrhythmia is present in the dog. Only when the CO_2 is washed out does arrhythmia occur. Recently they have increased the concentration of CO_2 to 75%, with the same effect. The CO_2 tension at this stage is as high as 600 mm. Hg. and the pH is 6.2. The significance of this work is not yet clear. One explanation given by Dr. Graham for the breathing to be present at such high percentages of CO_2 is that, although the respiratory centre in the

medulla is completely depressed at this stage, the gasping centre is still active. These workers are now hoping to try by further experiments to find out if any brain damage occurs as a result of subjecting these dogs to such high concentrations of CO_2. In any case, it makes one wonder if the small accumulations of CO_2 occurring in anaesthesia are as harmful as was once thought to be the case.

Professor Woolmer has also performed interesting work on the minute volume during anaesthesia. He invited various experienced anaesthetists to squeeze the bag as they usually do during controlled ventilation whilst he took continuous spirograms. The findings showed that the minute volume varied from person to person and that most erred on the side of increased minute volume. This is one of the arguments in favour of artificial ventilation by machine, especially in prolonged cases of controlled ventilation.

London Hospital. Two interesting cases, of one-lung anaesthesia by Parry Brown, were observed. In the first case a Vernon Thompson blocker was used to obtain left lung anaesthesia for a right pneumonectomy. After induction Parry Brown favours injection of 2 c.c. 4% Zylocaine through the crico-thyroid membrane before giving relaxant and intubating.

In the next case the operation was for an upper left lobectomy. The induction was the same as in the previous case, but the one-lung anaesthesia was carried out by means of a Carlen's tube. To test for the correct position of the tube, a pair of forceps was applied to the right proximal limb of the Carlen's tube, the Cobb's connexion cap was removed, and the lungs inflated. Very little gas should escape from the right lung if the tube is snugly in position and the cuffs properly inflated. In this case there was a rather large escape of gas until the right bronchial cuff was further inflated. The chest should also be auscultated for evidence of proper air entry.

One-lung anaesthesia is only used after opening of the pleura.

The advantages claimed for this method are that the secretions can be properly controlled without interrupting the anaesthesia and that the mediastinum is held up. The surgeon can work on an immobile deflated lung and bronchial fistula is no problem. If necessary, intermittent doses of Pethidine are also given. Parry Brown maintains that if the blood pressure falls and the pulse increases in spite of adequate blood replacement, more analgesic is required.

The Western Hospital, London. The greatest number of patients suffering from respiratory failure in England are treated here. To visit the Respiratory Unit under the very capable management of Dr. Kelaher is indeed an experience. The 'dry' cases with complete respiratory paralysis are placed in a tank respirator. Each case is treated daily by a physiotherapist who applies pummelling of the chest in the prone position; the patient is encouraged to cough during this procedure. Dr. Kelaher has invented a rotating iron lung for this purpose.

The 'wet' cases are treated first by performing a tracheotomy and then by ventilating with a Radcliffe machine.

In other cases where respiratory paralysis is not complete the Eve rocking bed is used. It is quite amazing how accustomed patients can become to these rocking beds. They even read and sleep during the rocking. If they feel any respiratory embarrassment, they can switch on the rocking. Tidal volumes are measured from time to time and as these improve the patients are given a rest from rocking.

Every aspect of the patients' care is considered. The female patients are 'made up' each morning and those who are interested in books have somebody to read to them.

The Nuffield Department of Anaesthesia, Oxford. At this great centre a great deal of research is being done in clinical anaesthesia under the guidance of Sir Robert McIntosh and, on the physical side, by Dr. Epstein.

A very popular technique here is the air-ether mixture administered by the E.M.O. machine. This is the ideal technique for the occasional anaesthetist as well as for the specialist who is practising away from a big centre where the supply of nitrous oxide and oxygen is not dependable. The usual induction is used and about 8% ether and air given until the patient is settled; and then gradually reduced to between 2-3% for maintenance. In cases where controlled ventilation is desired, this can readily be done by giving the required relaxant and inflating with the Oxford inflating bellows. Diathermy can be used with this anaesthetic, as ether and air in these percentages is not explosible, according to the Oxford workers. Most of the patients are awake at the end of the operation and no cases of nausea or vomiting were seen following these anaesthetics.

A disadvantage of this method, however, is that if Scoline is used and the patient inflated only with air before intubation, anoxia will

occur if this manoeuvre is not carried out rapidly. Azeotropic mixtures of ether and Halothane are also being tried out here. The only advantage of this mixture appears to be that it is more economical than Halothane and that it induces greater relaxation.

A favourite endotracheal tube used here is the L-shaped Oxford tube. It remains more firmly anchored in the trachea once it is passed and the distal part rests snugly in the trachea without any danger of the bevel becoming wedged against the trachea. In small babies it is thought to be ideal because, in the first place, there is very little chance of its slipping down into the bronchus and, secondly, there is very little likelihood of its becoming dislodged once it is fixed in place.

At present there is a swing away from the use of CO_2 absorbers at Oxford. The disadvantages, such as the unreliability of the soda lime, the heating up of the canisters, and the incidence of bronchitis, can be overcome by using other techniques. The non-return valves, such as the Ruben and Mitchell types, are much in use to prevent CO_2 accumulation. A technique also used, and which may invoke criticism in certain quarters, is to control ventilation by means of a big minute volume of gases and the squeezing of the bag with a partially opened Magill expiratory valve in the Boyle's machine, no absorber being used.

About 25% of all anaesthetics administered here are by the regional method. The surgeons display a great degree of indulgence and no anaesthetist is ever hurried. There is no doubt that there is still a place for regional anaesthesia if the conditions are as ideal as they are at Oxford.

Oxford is also fortunate in having Dr. Epstein, who has a very fine laboratory in which he studies aspects of physics in relation to anaesthesia. Equipment used for anaesthesia is checked for accuracy and a most elaborate refractometer is used for measuring the percentage of various gases. Mr. Salt is in charge of the workshops where the anaesthetic equipment is checked and repaired. Work is continually being carried out in trying to improve on present equipment and even inventing completely new apparatus. For instance, the E.M.O. machine has been calibrated for Halothane and for azeotropic mixtures. Work is also being done in trying to improve the Mitchell non-return valve.

Cardiff. The Anaesthetic Department is under the direction of Professor Mushin. A great deal of research work is being done. The physical aspects are under the care of Mapleson and Hilliard. Here, as elsewhere in Great Britain, the impression is gained that the Anaesthetic Department is very important, well staffed and well organized. It is not only a Department for supplying anaesthetists for the various surgeons; but it is also actively engaged in the task of solving the different problems and improving the standard of anaesthesia.

An interesting problem in anaesthesia was demonstrated by Professor Mushin.

An obese female 77 years old had to undergo an operation for retrosternal goitre causing pressure and partial obstruction of the trachea. The induction was administered by inhalation of Halothane, spraying the throat and intubating after injecting 25 mg. Scoline. Holes were cut into the distal end of the tube in case it entered the bronchus. If this did happen the opposite lung would still be ventilated.

Two cases for laminectomy were anaesthetized by Peter Thompson. He used a combination of Fluothane and Arfonad to obtain a bloodless field. The respiration was rather depressed, as evidenced by the diminished respiratory excursions. No assistance of respiration was attempted. The explanation given for this attitude is that during Fluothane anaesthesia the CO_2 production in the body is diminished by as much as 30%. The minute volume accordingly can be lessened without causing CO_2 build-up.

Galloon is a protagonist of controlled ventilation for neuro-surgical anaesthesia. In cases of cerebral aneurysm he often combines it with hypothermia. He claims that very little bleeding occurs with this technique. The hypothermia is accomplished by applying ice packs to the patient.

A discussion on cardiac arrest by the Welsh Surgical Society revealed some interesting points. The most common cause of this catastrophe is vomiting followed by overdosage of Pentothal. Mushin stated that if it did occur during intubation it was due to faulty technique.

It was also agreed at this meeting that the only adequate way of carrying out cardiac massage is by the trans-thoracic method. Cardiac massage cannot be as efficiently performed through the abdominal route. If the anaesthetist is in doubt whether cardiac arrest had occurred, he must immediately ask the surgeon to make a one inch incision in the chest wall and, if no bleeding then occurs, he must proceed with cardiac massage.

(*To be concluded*)

ACUTE RENAL FAILURE

ASSOCIATED WITH THE MANAGEMENT OF DIABETIC COMA

REPORT OF AN UNUSUAL CASE

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Acute renal failure usually occurs after such obstetric complications as accidental haemorrhage and septic abortion, but also follows incompatible blood transfusion, blackwater fever, severe trauma, surgical operations and the administration of kidney poisons, e.g. mercury. The present report of a case of acute renal failure associated with the management of diabetic coma seems warranted not only because of its unusual cause but also because of the clinical problems which arose in treatment.

Mrs. X, aged 56, was referred to this hospital for admission at 1 a.m. on 25 May 1960. According to the note which accompanied the patient, she had been in diabetic coma since 6 p.m. the previous evening. She was a known diabetic who had had remissions of long duration, and exacerbations with infection. The precipitating cause of the present attack was not known. At 8 a.m. the day before admission she was given 30 units of protamine zinc insulin and at 6 p.m., when the urine was brick-coloured on testing for sugar, a further 10 units of soluble insulin. Apparently to combat a deepening coma, 400 units of soluble insulin were injected at 7.45 p.m., and another 180 units at 11 p.m.

Also at this time, because no Vacoliter of normal saline was available, an intravenous infusion was set up of sterile, pyrogen-free *water*. She was transferred to this hospital with the infusion still running and, by the time she came under our care, it appeared that she had received a total of 1,700 ml. of intravenous water.

The water was immediately discontinued and a solution of dextrose-water substituted. The patient, an obese, middle-aged female, was not in coma and responded readily to questions. Her general condition was satisfactory (blood pressure 140/90 mm. Hg.; pulse 72 per minute; respirations, 22 per minute; temperature 94.6° F.) and there was no evidence of acidosis. She was, however, sweating slightly. A catheter specimen of urine was very dark in colour, and microscopy revealed numerous red blood cells and red cell casts. Sugar was absent. Initial blood estimations gave the following information:

Blood sugar: 89 mg. per 100 ml.
Blood haemoglobin: 11 g. %.
Plasma haemoglobin: 21.6 mg. %.
Serum potassium: 5.05 mEq./L.
Serum sodium: 152.3 mEq./L.

Her total urinary output during the first 12 hours of admission was less than 60 ml. of dark, blood-stained urine. Further blood investigations confirmed the previous high plasma haemoglobin level, the 9 a.m. reading on 25 May being 30 mg. %. This level dropped over the next 24 hours to 11 mg. % and then to 6 mg. %, indicating that no further intravascular haemolysis was taking place. The serum potassium at 9 a.m. had risen to 8.2 mEq./L., but following the institution of treatment fell to normal limits. The blood sugar remained unchanged at 89 mg. per 100 ml. The blood urea rose from 48 mg. per 100 ml. in the morning to 90 mg. per 100 ml. that evening.

Because of her obesity, an attempt at paravertebral block to relieve renal ischaemia failed, nor was a successful low spinal anaesthetic rewarded by diuresis. It was decided to treat her as a case of acute tubular necrosis. A polythene cannula was inserted through an arm vein into the superior vena cava, but could not be made to run satisfactorily. The long saphenous vein was therefore exposed through a Trendelenburg incision high up on the thigh, local anaesthesia being used, and the polythene cannula inserted through the vein into the inferior vena cava, where it continued to function with minimal trouble or discomfort for the next 15 days. A solution of 40% dextrose in water was started, penicillin (100,000 units) and heparin (1,000 units) being added to each bottle. No more than 1,000 ml. of the dextrose solution was to be given in each 24-hour period. To counter protein break-

down, 25 mg. of an anabolic steroid (Durabolin) were administered initially 3 times daily by intramuscular injection. Subsequently the injection was given twice weekly until the recovery of renal function. One injection of streptomycin (0.5 g.) was given intramuscularly.

At the time of starting the caval infusion, her general metabolic state was satisfactory, except for a low carbon dioxide combining power of 15.5 mEq./L. This occasioned some concern, especially as the patient was now complaining of nausea and tended to retch. No specific treatment for her acidosis was, however, instituted.

Despite slow infusion of the hypertonic glucose solution, the blood sugar rose rapidly during the afternoon and evening of 25 May to reach a level of 596 mg. per 100 ml. at 10 p.m. At this time, her carbon dioxide combining power was 20.7 mEq./L. To control the hyperglycaemia, 50 units of soluble insulin were given hypodermically and 100 units added to the drip. The blood sugar dropped to 350 mg. per 100 ml. 2 hours later at midnight, only to rise again by 8 a.m. on the morning of 26 May to 555 mg. per 100 ml. Acetone tests on both plasma and the small available amount of urine were at all times negative and there did not appear to be great danger of ketosis. However, a further hypodermic injection of soluble insulin (100 units) was given. At this stage (the morning of the 26th), the patient seemed reasonably well, although nausea still persisted. Nothing had been given by mouth, and about 700 ml. of the first Vacoliter of hypertonic glucose had been administered. Total urinary output for the previous 24 hours was 53 ml. The urine was still dark in colour with an obvious red cell deposit.

By midday on the 26th, the blood sugar had dropped to 210 mg. per 100 ml. It was decided that her diabetes would probably best be controlled by giving one unit of insulin for every 2 g. of sugar. Consequently, 200 units of soluble insulin were added to the second Vacoliter of hypertonic glucose, the other additions being, as before, penicillin and heparin. Later, a multi-vitamin preparation containing thiamine, vitamin B_2, vitamin B_6, calcium pantothenate, nicotinamide, vitamin C and vitamin B_{12} was added to each vacoliter.

Blood sugars during the night of 26 May ranged between 177 and 325 mg. per 100 ml., and for the rest of the oliguric and early recovery phases this amount of insulin added to the 40% dextrose solution controlled the hyperglycaemia reasonably well at a level usually between 300 and 400 mg. per 100 ml.

She remained in good metabolic balance for the next 4 days. The blood urea, as expected, steadily rose each day by about 20 mg. per 100 ml., but blood electrolytes were within normal limits. Indeed, the potassium level never at any time during her subsequent hospital stay rose above the upper limit of normal. Urinary output during these 4 days remained low, the 24-hour totals being 135 ml., 113 ml., 270 ml. and 204 ml. Nausea did present a difficulty in management, and on 30 May the patient began retching and vomiting persistently, bringing up a few ml. of clear fluid on each occasion. The serum sodium now fell to 121.8 mEq./L. The next day the serum sodium fell still further to 113.1 mEq./L. At about the same time, the carbon dioxide combining power also fell, first to 20.7 and then to 15.9 mEq./L.

Replacement of the sodium chloride intravenously presented a difficult problem. Five per cent sodium chloride solutions were not available, and to replace the estimated deficit of about 26 g. NaCl (450 milli-equivalents) with normal saline solution would have required almost 3 litres of fluid, this at a time when her total 24-hour urinary output was 285 ml. In the end an attempt was made to give NaCl in the form of oral capsules, despite the danger that this might increase the vomiting. Vomiting did increase, but even so sufficient NaCl was absorbed to restore the serum sodium to more normal levels, the figure rising to 135 mEq./L. on 1 June. Continued oral administration maintained the level at this figure for the next few days. Renal conservation of sodium was also taking place because analysis of the 24-hour specimens of urine during this time gave readings of 55, 85 and 110 mg. per 100 ml. The carbon dioxide combining power, however, remained low, ranging between 15 and 17 mEq./L. Without specific treatment, the level gradually rose to 20 mEq./L., but did not return completely to normal until late in her convalescence.

The basic intravenous intake of 1,000 ml. per day was continued, additional fluids being given orally to keep pace with urinary secretion. A urinary output of 300 ml. was achieved first on 2 June (9th hospital day). While the urinary urea was initially low, it rose steadily from 0.6 g. per litre to 1.1 g. per litre on 7 June (14th hospital day). The blood urea reached its highest peak of 234 mg. per 100 ml. on 3 June and thereafter began to fall steadily. As it did so, urinary sodium, potas-

sium and calcium all rose more or less steadily to normal levels. The initial low urinary phosphorus levels (12, 16, 14, 18 mg. per 100 ml.) rose to 37 and 40 mg. per 100 ml. and then fell to normal levels.

During this stage of recovery there were occasional incidents to mar the generally satisfactory pattern. On 7 June she developed a marked skin erythema, particularly over the chest and in the scar of an old wound in her right arm. The intravenous penicillin was discontinued and on anthistaminic treatment the rash subsided. Also, with the recovery of renal function the adequate control of her diabetes by the administration of one unit of insulin to 2.0 g. of glucose (200 units in the Vacoliter containing 400 g. of glucose) became less satisfactory. The blood sugar fell on 9 June to 115 mg. per 100 ml., but rose to 185 mg. per 100 ml. the next day.

On 11 June she felt faint and dizzy and seemed to be developing a hypoglycaemic state. At this point the urinary output reached 2,000 ml. in 24 hours for the first time, but both specific gravity and urinary urea were still low. The insulin in the drip was reduced to 150 units, but despite this on the evening of the 11th she had a marked hypoglycaemic episode. Insulin was therefore completely discontinued and the next day the drip into the vena cava was also stopped, since she was now almost completely free of nausea and could take adequate food and fluids by mouth. She was placed on a 1,600 calorie diabetic diet and careful watch kept on both urine and blood sugar to ensure that marked hyperglycaemia did not recur. In fact, no further insulin proved necessary, the blood sugar levels during the rest of her hospital stay remaining between 250 and 300 mg. per 100 ml., and the urine showing nothing more than occasional traces of sugar.

On 16 June (23rd hospital day), a haemoglobin estimation showed a mild normochromic anaemia (9.8 g. %). Two pints of blood were therefore transfused, but the level 2 days later was only 10.6 g. %. Otherwise, her general improvement continued, and she was discharged from hospital on 23 June. The blood urea on this day had dropped to 50 mg. per 100 ml., and the urinary urea was now 1.9 g. %. All the other biochemical investigations were normal.

Subsequently, she developed 2 episodes of acute mucous diarrhoea, attributed to the iron tablets she had been instructed to take. When seen 2 weeks after discharge, she was in good health. The diabetes was still being adequately controlled on diet (blood sugar 325 mg. per 100 ml.) and, although the blood urea was still raised (40 mg. per 100 ml.), her renal function was otherwise satisfactory.

COMMENT

According to Wintrobe[1], 'the entry of 600 ml. or more of water into the circulation will produce haemoglobinaemia and haemoglobinuria'. The sequence of events in this patient would therefore appear to be:

(*a*) Administration of a large quantity of intravenous water.

(*b*) Acute intravascular haemolysis with release of excess amounts of haemoglobin.

(*c*) Renal damage, resulting either from blockage of the tubules with haemoglobin casts or from renal ischaemia.

(*d*) Acute tubular necrosis.

The exact mechanism of acute renal failure is still disputed. Intense and prolonged renal vasoconstriction is known to occur with a fall in circulating volume, especially if there is a simultaneous fall in blood pressure. In our patient, so far as is known, a marked degree of shock was never present. The other possible mechanism which suggests itself is blockage of the tubules by haemoglobin or its derivatives. But Miller and McDonald[2] found that even large amounts of free haemoglobin in the plasma did not affect renal blood flow in normal subjects. Even so, acute tubular necrosis is a recognized complication of incompatible blood transfusion, following on acute intravascular haemolysis and release of excess haemoglobin into the plasma; and, whether the mechanism is primarily ischaemic or obstructive or a summation of both factors, our patient obviously followed the same pattern. The cause of the blood destruction is, however, a most unusual one.

Management of the oliguria presented certain difficulties. Obviously, oral methods were best avoided. Even in favourable circumstances, the indwelling gastric tube becomes irritating after a few days, and the inevitable rise in blood urea is often associated with increasing gastro-intestinal disturbances. The diabetes would have made the possibility of vomiting still more likely. Also, control of the diabetes was more easily accomplished by intravenous feeding.

Perhaps the most striking feature of the oliguric phase was the serum potassium level which, after its initial peak of 8.2 mEq./L., never rose above normal limits, despite considerable intravascular haemolysis. In association with a high glucose intake, insulin tends to draw potassium into the cells, thus lowering

the serum potassium level. It is interesting to speculate whether a marked rise in serum potassium and, perhaps, a subsequent need for dialysis might not have occurred had this patient not required large amounts of insulin for the control of her diabetes. It is also interesting to note the marked and sudden drop in insulin requirements as complete recovery of renal function began; so much so, that a hypoglycaemic episode occurred despite a reduction in insulin dosage. Indeed, insulin could be discontinued thereafter and the diabetes controlled solely by diet.

Criticism might be directed at the giving of as much as 1,000 ml. of water every 24 hours, especially since current practice[3] is to restrict basic fluid intake to 600 ml. per day or even less. However, this patient was obese and tended to perspire freely in a hot climate; so more liberal quantities of fluid seemed indicated. The administration of sodium chloride during the oliguric phase might similarly be censured, as low serum levels for sodium are more likely to be due to intracellular movement of sodium, metabolic readjustments of of fluid tonicity or dilution of serum sodium by excess water, either from metabolism or administration[4]. Although there was no direct evidence at this time that there was excess loss of sodium either in sweat or in urine (indeed, the urinary sodium was only 55 mg. %), we felt that the continued fall in the serum level coupled with her retching warranted an effort at control, and sodium chloride was given orally with good effect.

SUMMARY

A case is reported of acute tubular necrosis associated with the management of diabetic coma, the condition apparently following the administration of intravenous water in large quantities.

A polythene cannula was inserted into the inferior vena cava and satisfactory treatment achieved by hypertonic (40%) glucose, one unit of insulin being given for every 2.0 g. of glucose.

It is thought that the high dosage of insulin required for the control of the diabetes contributed to the management of the renal failure by drawing potassium into the cells and so preventing a possibly dangerous rise in serum potassium.

We would like to thank Dr. Kidd, under whom this patient was originally admitted, for permission to treat her, and Dr. D. L. Ranking, Medical Superintendent, for permission to submit this paper for publication. We also owe a debt of gratitude to Sister McKay and the staff of Nathan Ward for the meticulous nursing care the patient received and to the laboratory staff for their unfailing help and co-operation.

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ENDOSCOPY OF THE BILIARY DUCTS

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(*Concluded from p.* 516)

VIII. CHOLANGIOGRAPHY OR ENDOSCOPY OF THE BILIARY DUCTS

It is impossible to review the whole literature on cholangiography which has appeared during the last few years but undoubtedly cholangiography has considerably advanced the diagnosis of intra- and extra-hepatic affections with stones in the biliary ducts. But there is also no doubt that with this method some stones cannot be made out. Norman only found 31 of 46 hepatic stones by using operative cholangiography. This also stresses the value of endoscopy opposed to cholangiography. I share Schega's view that the uncertainty of this method must be attributed to the fact that stones can only be recognized in an indirect way; at best they are seen as a negative shadow in the radio-opaque material and very often intra-hepatic stones which lie very deeply cannot be found, as is also proved by Norman's observations. Therefore a wrong diagnosis is easily made. Besides very good X-ray conditions, great personal experience is necessary and I dare say that nowadays cholangiography has become in most cases superfluous though I appreciate the great value cholangiography has had in the past. According to my experience, the combination of both methods, endoscopy and cholangiography, is in most

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cases not acceptable. The operation is unnecessarily prolonged. In 100 cases I used cholangiography only 3 times additionally. If the common duct shows an abnormal course or if it is distorted in so far as the view is not good or not complete, i.e. if in some cases one does not get up to the papilla with the instrument, cholangiography can be employed additionally. Cholangiography may also become necessary to control the right position of the T-drain. But if I can convince myself in a case with good visualization that the biliary ducts are really completely free of stones, from the deep liver ducts up to the papilla, cholangiography is superfluous. My further statements will also show that endoscopy is of greater value than cholangiography.

IX. RESULT OF THE FIRST 300 ENDOSCOPIES TREATING 127 PATIENTS

Three hundred endoscopies were carried out on 127 patients.

Of 127 patients in 66 cases icterus appeared during the operation; in 26 cases an intermittent icterus was found and in 35 cases the patients did not have any icterus.

In 68 cases operative endoscopy was carried out only once. In the case of 59 patients one had to insert the instrument several times. In the case of a 51-year-old patient ill with icterus, 44 stones were removed from the biliary ducts. One had to insert the instrument 15 times to clean the ducs from all stone crumbles and stone particles. In spite of using all instruments and of washing it was not possible to catch and to remove a stone rest that lay too deep in the hepatic duct.

In 3 of our 127 cases we had to leave behind a very small hepatic stone because in these 3 cases it was impossible to remove it though we used all auxiliary means. We treated these cases with a corresponding T-drainage and tried to decompose and to remove the stone by washing several times with Pribram or Seneque lotion. In the following period we were not able to make out the stone by using cholangiography. This does not at all signify that the stone had really decomposed and been removed.

Most interesting is the fact that we found completely unexpected results in 57 cases. We planned a cholecystectomy with a patient who has never been jaundiced and succeeded in removing the gall bladder which was filled with stones. The pancreatic head seemed to be rather hard; endoscopy through the cystic duct was easily possible and we found a chain of stones which lay jammed before the papilla in diverticular evaginations. By making great efforts it was possible to clean the common duct of all stones and because of the changes in the duct a T-drain was put in. Instead of the cholecystectomy which had been planned we had to use the choledochotomy with T-drainage.

With 37 patients we had to change the original operation plan, as may also be seen in the Table. While formerly in many cases one applied choledochoduodenostomy or T-drainage in cases of stones or of gall grit or gall mud, to-day we can eliminate these if we can state with endoscopy that the ducts are really free of stones and if the papilla does not show any great changes and the mucosa no greater inflammatory changes. In this case, one may suppose that the mud and the stones originate from the gall bladder and therefore one can close the duct after the inspection if the already mentioned conditions of the duct and of the papilla are fulfilled. As Schega stresses rightly, the choledochoduodenostomy which is often employed because of an uncertain feeling has become superfluous.

Among our patients there are 16 operated on whose ducts or better whose cystic stumps could again be sewed up after careful visual control. In none of these cases did any complications arise. In all these 16 cases we would have applied a drain or an anastomosis before the invention of the endoscope. If one finds much mud in the deep intra-hepatic biliary ducts which are inflamed one has to suppose that in these rare cases perhaps part of the stone formation really took place in the biliary ducts. Then I continue to use the choledochoduodenostomy in order to facilitate the elimination of the mud masses. On only 3 occasions did we decide for these reasons to create a wide connexion to the duodenum. An anastomosis is further advisable in the rare cases in which stones or stone splinters and rests which have been seen with the endoscope have to be left behind in the ducts because they cannot be removed at all.

In such a situation I am of the opinion that it depends on the state of the papilla, on the form, size and width of the biliary duct as well as on the position of the concretion and on the nature of the mucosa of the common duct if a choledochoduodenostomy is necessary or if a drain in the common duct is sufficient. The width of the T-drain to be put in, the duration of T-drainage, already laid in, the time of the first pinching of the drainage, the possible replacing of the bile into the intestine with the Mollowitz sound, these all depend completely on the

diagnosis made by inspection of the biliary duct and the papilla and are no longer subject to a certain schematism, as in former times.

At this point we again notice the great advantage which endoscopy has over the cholangiography because the little changes in the biliary ducts and the papilla can only be seen with the endoscope. In lithiasis not only the position and the actual count of the number of stones matters, but above all the surroundings, i.e. if the biliary ducts and the papilla are also affected or not and if so in which manner they are inflammatory. In one patient we saw actual pus running from the deepest hepatic ducts, so that besides lithiasis in the gall bladder and the biliary ducts we had to diagnose an intra-hepatic abscess. This proved to be right—the patient died.

Generally the visual conditions are good or very good. Bad vision has either to be attributed to the imperfect unfolding of the biliary duct so that the flushing liquid has to be poured in under a somewhat stronger pressure or it has to be attributed to inflammatory swellings of the mucosa; therefore one cannot make the method responsible for the bad field of vision. Of 127 cases in which we carried out endoscopy, in only 6 cases was it not satisfactory. Either we found doublings of the common duct caused by a pancreatic tumour or, in another case, there was such an adiposity that we could not inspect the common duct with the instrument with the large branches. To-day this disadvantage has been eliminated because of the short branches.

With the first 49 cleanings of the common duct with the formerly usual instruments, endoscopy carried out after the cleaning resulted only in 18 cases completely free of stones. In 31 cases after the mechanically executed cleaning, additional concretions were seen. We therefore decided to apply endoscopy from the beginning, i.e. in cases of stones we at once inform ourselves of the conditions in the biliary ducts with the endoscope and only then begin to clean stones from the duct partly with the already mentioned instruments partly without any optical control.

IXA. EXACT LOCALIZATION OF THE STONES FOUND BY ENDOSCOPY IN THE BILIARY DUCT

TABLE 1

Patients with Concretions Proved by Endoscopy:	59
In the Common Duct:	40
Near the Papilla:	15
Supra- or Retro-Duodenal:	25
In Both Ducts:	7
In the Hepatic Duct:	12

Of the 59 patients with concretions found by endoscopy, 15 were in the common duct near the papilla and 25 supra- and retro-duodenal. In both ducts, i.e. in the common duct and in the hepatic duct, stones were found in 7 cases; while in the hepatic duct stones were found 12 times. Most of the stones in the common duct lay in the supra- and retro-duodenal part. Sometimes one cannot exactly localize the stones which lie in the deep common duct because they very often change their position and swim freely movable in the biliary duct. Often one can also see little stones like pebbles floating in the flushing liquid.

One does not always succeed immediately in making all concretions visible which lie in the field of vision, because many stones may be strung one behind the other in a chain so that the rear stones are completely hidden by those lying in front. Also confusion with blood clots occurs. Sometimes one can recognize the stones with difficulty because they are wrapped up in fibrin and slimy flakes, so that it is impossible to distinguish them from a real fibrin coagulum. Comparatively often one sees, however, that the stones just before the papilla lie in a diverticular bulge and tightly stuck together with the base, so that great efforts are necessary to loosen and remove them. If these stones lie directly in front of the papilla and it is impossible to remove them with a sling or pincers from the choledochotomy wound it is also possible to push the stones with an instrument, e.g. with pincers, through the papilla into the duodenum while observing the procedure with the eye. Such a stone depot in which a stone lay for some time may show an ulcerated, damaged mucosa with haemorrhagic infiltration and a partly fibrinous and suppurative covering. In a case of blind sounding one passes just these diverticular stones and supposes that there are no stones. We found such diverticular bulgings 7 times in a distinctly marked form in patients examined with the endoscope. The survey over a straight and not inflamed duct from the hepatic duct to the papilla and to the duodenum is very easy, but the appearance of very inflamed biliary ducts filled with fibrin and pus can be very strange and the search therefore very difficult.

I have already mentioned that some stones can only be removed in an extremely complicated way. Such difficulties can arise that one has to leave stones behind deep in the liver, as was demonstrated by the example already mentioned. We only succeeded in removing a stone that lay deep in the liver after electric slitting of the hepatic duct and levering of the

stone by means of a needle electrode. Wildegans states that after careful pathological and anatomical studies, hepatic stones were found in 8–10% of all gall stone cases which were autopsied. Norman, who employs cholangiography, found hepatic stones in 5.3% of cholecystectomies and in 23.6% of all stones in the biliary ducts. By the same method Hess found stones in the hepatic duct in 3.7% of all cases and in 15.7% of the cases with stones in the biliary duct, whereby two-thirds were said to be intrahepatic and only one-third lay in the common hepatic duct. The statement of Kourias is very informative. He found that in 8 of 16 cases in which stones were left, re-operations revealed the stones to have been in the hepatic and in the intrahepatic ducts.

IXB. INFLAMMATION OF THE BILIARY DUCTS

Cholangitis without stones is only seldom seen. Generally the haematogenously metastatic inflammation only appears if the sides of the ducts are either damaged by direct influence of the stones or indirectly by too long obstruction. The appearance of the cholangitis changes from the light catarrhal form, through the fibrinous inflammation to the grave necrosing inflammation of the biliary ducts. If the inflammatory changes also affect the smaller ducts, cholangiolitis results with the danger of damaging the liver-epithelium and finally this may result in a cirrhosis of the liver. Prompt diagnosis and sufficient medical attention may eliminate a further aggravation as well as the remaining pains after the operation. *Only with the endoscope can one state to some extent the severity, grade and extent of the inflammation.*

In milder cases hyperaemic swellings of the mucosa or simple oedematous swellings are seen. The graver form is characterized by cloud-like fibrinous coagula which are connected with the sides or float in the flushing liquid. In case of suppurative cholangitis one comes across festering, fibrinous coverings which are either localized in the part of the passage system in which stones have lain or they are spread all over the inner lining. In one case we saw a severe necrosing inflammation with the endoscope which, besides haemorrhagic extravasations of blood and loosened rags of the mucosa, showed multiple pin-size ulcers at the sides of the biliary ducts. In all, 30 of our 127 patients had an inflammation of the biliary ducts. About half of these cases were of a milder nature while the other half showed graver inflammatory changes.

IXC. PAPILLITIS

Besides the cholangitis, the aspect of papillitis (particularly stenosing papillitis) deserves special consideration. Of course it is already known but during recent times it has won much interest because of the introduction of modern examination methods. Histologically it is (according to Hess) a sclerosis of the sphincter muscle and of the surrounding mucosa and submucosa. Additionally more or less developed acute inflammatory infiltrations of the mucosa are found and often a marked hyperplasia of the glands in the part round the papilla. Thorough intra-operative radiological examinations of the biliary ducts with radio-opaque material have shown that the stenosis restricts itself always to the intramural part of the common duct, but its elongation varies very much because either the whole Oddi's sphincter or only a part of it can be included in the cicatrization. If the stenosis is fully developed only in the inferior part of the sphincter ampullae, it is the rather short, so-called pylorulus stenosis. The suprapapillary common duct is, in cases of papillitis, considerably widened. One nearly always comes across a stenosing papillitis only if at the same time also other abnormal changes in the biliary ducts exist.

In most cases it is accompanied by a choledocholithiasis. But we have found it also in cases of a simple stone gall bladder and a chronic cholecystitis. First of all it has to be considered as a complication of the lithiasis. As Hess also expresses it, these conditions have to be looked upon as secondary papillitides. A primary papillitis in which the whole biliary system is unaffected is extremely rare but has a practical importance in so far as it may be mixed up diagnostically with a stone closure of the common duct and therefore it has of course to be treated correspondingly. Nothing is known confidently about the cause of the primary papillitis. Sometimes one finds a mild pancreopathy, a duodenal ulcer, duodenal diverticula or a duodenitis, so that these illnesses are taken to be the reason for the papillitis.

Nothing definite is known about the mechanism of the secondary papillitis. In many cases the direct influence of the stones on the papilla may cause its damage and later the scarred stenosis of the sphincter region may result. Also the simple stone gall bladder causes the secondary papillitis whereby even the cystic duct can be obliterated or big concretions can be enclosed in a shrunken bladder. These are cases in which no stone has passed the papilla so that Hess asks whether a stone

illness must precede an affection of the papilla. It could also be on the contrary, that the inflammatory narrowing of the papillary region promotes only secondarily the stone formation in the distal parts of the biliary ducts. Mallet-Guy gives both forms of the papillitis the name of *maladie du sphincter* and sees in them the organic manifestation of a disturbance in the tone regulation of the sphincter muscle, while a longer lasting sphincter hypertension finally takes the form of a stenosis.

Though one cannot disprove the different views of the cause of a stenosing papillitis, the most frequent reason seems to be the direct effect of the lithiasis or the inflammatory changes in the biliary system. Shrinkages happen in the region of the whole gall bladder and of the cystic duct, and inflammations may appear at this narrow point of the papilla which then cause a corresponding impediment to evacuation. This inflammatory narrowing of the papilla is only important because the spontaneous flux of concretions in the common duct can be prevented. On the other hand, post-operative complaints, colics and slight icterus may be maintained by a poorly treated papillitis.

There are many different opinions about the frequency of this papillitis. Hess supposes that it appears in more than one quarter of all operations on the biliary ducts; he finds it in 63.6% if a second laparotomy is carried out because of colic. Wildegans makes quite different statements. He made the diagnosis of stenosing papillitis with the endoscope in only 4 of 51 patients operated on and thinks that in most cases it is a more or less developed acute inflammatory infiltration of the whole common duct with a tendency to spasm and stiffness of the walls. This appears to be a papillitis in the radiological picture and he thus explains the unusually high quota of the pipallitides which have been diagnosed by cholangiography.

According to my experience the papilla is only involved if the common duct or the hepatic and the common duct also show inflammation. To what extent one can call it a true stenosing papillitis in the different cases is rather subjective. If I see a papillary swelling of an oedematous nature and remove the obstruction, the stone, and thereby eliminate the permanent irritation on the mucosa, I suppose that the narrowing at the papilla will be soon remedied; and thus it can be explained why some authors diagnose such a papillitis very frequently while others diagnose it only in few cases. In our patients changes at the papilla appeared on 40 occasions, i.e. in nearly one-third of all patients examined by endoscopy. Of these 40 patients we found a choledocholithiasis 20 times and in all the other cases a cholelithiasis with corresponding inflammatory changes of the walls. Only one patient showed a so-called primary papillitis and the rest of the biliary system was completely free of pathological changes. This patient was a 52-year-old woman with colic. Any sounding of the papilla was impossible even on direct inspection and no abnormal changes at the other parts of the biliary system could be found.

Visual examination of the processes in the papillary region has an advantage over indirect examination by cholangiography in that one can clearly control the morphology and the function of the papilla. One can see mechanically injured papillae with a torn and split mucosa, fibrin covered with escaping blood pointing to the passage of a stone which has just occurred or has happened a short time before; furthermore, we also see profound changes which allude to a longer lasting inflammatory process and which appear as oedematous swellings or as a scarred sclerosis in the papillary region. The question whether and how far a true stenosis has developed is very important in all these inflammations of the papilla. One can answer this question endoscopically very exactly if a fully functioning papilla presents itself. The endoscopical proof of a mobile papilla excludes, as Wildegans states, a stenosis of the papilla.

We have observed that not every papillitis is accompanied by a stenosis. Only in 10 of 40 cases did we find a real impediment of bile evacuation because of the inflammatory process in the region of the papilla, with distinct disturbances of the function of the sphincter. In all other cases of papillitis the function of the papilla was unimpaired or only very little disturbed so that one could not prove by inspection an injury and speak of a stenosis. One has to suppose that in these cases there are slight inflammatory changes which appear acutely and are caused by the mechanical irritating effect of the concretions which lie near the papilla. These changes remain without further regression in the distal parts of the biliary ducts. Very often one could not sufficiently make out the changes at the papilla and the ducts without endoscopy and therefore these have easily been mixed up with other conditions when examined by the usual methods. This passes especially for all evacuation obstructions which are not due to impaction but caused by tumourous changes of the walls in the region of the deflecting ducts.

Wildegans describes a case in which a lipoma the size of a small hazel-nut was found in the supra-papillary part of the common duct. This tumour caused a biliary obstruction which appeared clinically as an intermittent icterus. Generally the primary papillary carcinoma can be visualized very well, as the different cases show which I have already mentioned. We have only once seen a primary papillary carcinoma which we could diagnose and treat very successfully. It had developed into an empyema of the gall bladder and the common duct. The patient was treated by excision of the papilla and is still alive to-day after 3 years. Of the further factors which may cause a blockage of the lumen of the biliary duct I will only mention in addition the cicatricial stenoses resulting from prior operations, and those stenoses promoted by a chronic pancreatitis. Cicatricial stenoses generally prefer the region of the cystic stump (the supraduodenal part of the common duct) while chronic pancreatitis affects especially the intra-pancreatic part, as Hess has already stated.

IXd. Results Concerning Second Laparotomies

We performed a second laparotomy on 8 patients because of repeated colic or icterus. The first operations on these patients were carried out at a time when the endoscope had not yet been introduced. In 7 cases we found stones and in 3 cases an additional cholangitis was seen. In one case the necrosing inflammation of the biliary ducts was the only reason for the repeated appearance of the illness. Three times a papillitis together with a choledocholithiasis was noticed. It was difficult to distinguish whether in these cases the recent retention of bile was only caused by the inflammation of the papilla or together with it by a change in the position of stones.

IXe. Frequency of Diagnoses Made by Endoscopy in 127 Patients

Table 2 gives surveys of the endoscopic findings:

X. Disadvantages of the Method

At the end of my review I must point out some disadvantages. It may happen that a stone is overlooked because it is jammed between the attached tube and the sides of the biliary duct when inserting the instrument, so that one passes it with the instrument. This failure can be eliminated if one examines the whole space step by step while moving the endoscope slowly forwards and backwards and if one always tries to get a survey over greater parts of the biliary ducts.

These faults can of course be avoided if one has got enough experience with the endoscope. The discharge conduit of the main pancreatic duct can be seen very poorly with the endoscope. We have seen it very clearly only 3 times. I have already mentioned the danger of perforation of the posterior wall of the common duct in certain cases.

XI. Photography of the Biliary Ducts

During the last years some surgeons (Griessmann, Keller, Schega, Simon-Weidner) have made coloured photographs of the biliary system. They succeeded in producing really excellent illustrations of the different conditions. We used the photographic equipment of the firm, Wolf of Knittlingen, with a *Robotstarkamera* with a reflex top. This camera operates with a short over-charged tension and one gets enough light in the field of view at the moment of photography. Generally an exposure of 1/25 second is sufficient for taking photographs in the interior of the biliary ducts. In our experience Agfa film CK 17 has proved to be very good. It fulfils all requirements with reference to the focus. The number of useful photographs which can be taken, however, is relatively small compared with those that turned out less satisfactory. The photocholedochoscope has a rather thick calibre, so that it can only be used in case of very wide biliary ducts and therefore it is often impossible to lead the

TABLE 2

	Stones or Biliary Mud: 59	
In the Common Duct: 40	In the Common and Hepatic Ducts: 7	In the Hepatic Duct and its Branches: 12
Cholangitis and Cholangiolitis: Of a High Grade: 14	Of a Light Grade: 16	Intensely Widened Ducts: 35
Inflammation of the Papilla: Of a High Grade: 10	Of a Lighter Grade: 30	Papillitis with Choledocholithiasis: 20
Diverticula of the Common Duct: 7	Papillary Carcinoma: 1	Pancreatic Ostium Visible: 3

instrument sufficiently deeply into the liver in order to take photographs.

Endoscopy of the biliary ducts can be considered to mark great progress in biliary surgery and indicates that re-operations and complaints will be remarkably reduced.

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MILLI-OSMOLS MADE EASY

SOME FUNDAMENTAL BIOCHEMICAL AND CLINICAL CONSIDERATIONS

WITH PARTICULAR REFERENCE TO PAEDIATRICS

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(*Continued from p.* 510)

RENAL HOMEOSTASIS

Fig. 2 is useful for expressing the osmolar interrelationships and indicates the extent to which the kidney must concentrate in order to excrete the products of metabolism. It should be noted that the urinary constituents as illustrated in the figure do not apply to infants who are fully breast fed. They have a much lesser concentration of solutes in the urine, for breast milk contains comparatively little protein and salts.

In the plasma there are substances such as glucose, cholesterol, urea, creatinine, amino acids and others which have negligible osmolar functions. Glucose and urea, e.g. each exert osmolar forces of but 5 mOsm per litre of plasma. Glucose is completely reabsorbed in the kidney and does not appear in the urine. Urea is greatly concentrated in the urine. Plasma proteins are not filtered through, though amino acids are, in very minute urinary concentrations. Proteins expressed as g.% in the plasma can be converted to mM. per litre by multiplying by the factor 2.43. Plasma protein has an average valence of 8, so that the usual plasma concentration of 16 mEq. per litre is equivalent (as far as osmotic force is concerned) to 2 mOsm per litre. It is salutary to note that whereas sodium concentrations within the plasma are measured but as mg., and protein as g., as far as osmotic attraction is concerned, sodium exerts a force which is some 70 times that of the protein.

The kidney is the chief arbiter and adjuster of body homeostasis, though this is a function which it shares with the blood itself, the skin, the gut and the lungs, the latter being responsible for maintenance of plasma pH via agencies which are not of immediate concern here.

There are 5 mechanisms by which the kidney regulates fluid and electrolyte balance:

1. *Differential excretion and reabsorption of carbonic acid* (H_2CO_3)—a function which depends on the presence of the enzyme carbonic anhydrase within the tubular cells.

2. *Conservation of body base* by means of production of ammonium ions from amino acids within

the renal tubular system. The NH_4 is excreted together with an acid radical, leaving base free for reabsorption into the plasma. The adult excretes an average of 30–50 mM. per day of ammonia.

3. *Conservation of base* by means of excretion of acid phosphates in the urine when presented with alkaline phosphates from the plasma. Normally the plasma ratio of Na_2HPO_4 (alkaline phosphate) to NaH_2PO_4 (acid phosphate) is 5:1, but within the rural tubules, one H atom is made available to displace a Na atom, the latter returning to the plasma. In the urine the ratio of alkaline to acid phosphate is as 5:45 (1:9).

4. *Excretion of organic acids,* the normal adult disposing of some 25 mOsm daily.

5. *Excretion of base.* The body is protected against excessive loss of base by means of the reservoir supply of sodium within the bones. Some 10–30% of the body sodium is contained in bone, and about a third or a half of this is available for metabolism.

The excretion and reabsorption of water within the kidney is partly under the influence of the anti-diuretic (ADH) hormone secreted by the posterior pituitary gland. Normally some 80% of the water filtered through the glomeruli is reabsorbed via the proximal tubules. The 20% reaching the distal tubules is partially reabsorbed on the basis of ADH action. If there be much ADH, a great deal is resabsorbed and the urine is concentrated. With little ADH action on the tubules the urine remains dilute. ADH production depends, in turn, on water intake. With a high water intake ADH formation decreases so that the urine is dilute and increased in quantity. Corticoid secretions also affect tubular water reabsorption, but in opposite fashion to ADH. The process is poorly understood.

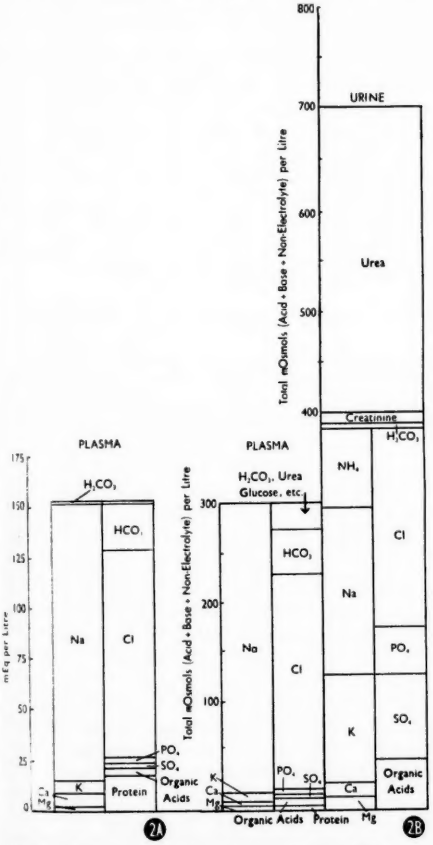

Fig. 2. Average Osmolar Concentrations of Solute in Plasma and Urine. (*Modified from* J. L. Gamble in *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid,* 1947, 5th ed., Chart 15. Harvard University Press.)

Within the glomeruli the hydrostatic pressure is in the order of 75 mm. Hg. To counteract this force there is the hydrostatic pressure within Bowman's capsule (10 mm. Hg) plus the attractive force of the plasma proteins (25 mm. Hg), a total of 35 mm. Hg. The effective filtration pressure tending to push fluids into Bowman's capsule is in the order of 40 mm. Hg. When systematic blood pressure decreases to very low values, then the effective filtration pressure may be decreased and anuria may result.

OSMOLAR LOADS

The osmolar loads presented for excretion by the kidney vary with the nature of the intake of food and salts. A bottle-fed infant has a Na intake some 5 times that of the breast-fed baby. However, this offers no protection against acidosis, for with the excessive Na there is also a concurrent increased intake of Cl, PO_4 and SO_4. The Na intake in breast-fed babies is of the order of 0.6 mM. per Kg., and in bottle-fed babies the daily intake of Na (and also of K and of Ca) is about 2.5–3.0 mM. per Kg. In the latter group the urine has a mOsmolar content some 5 times that of the breast-fed infant.[10] Nursing infants have an average of about 100 mOsm of solute per litre of urine, the pH of the urine also being higher. The greater osmolar content is due largely to a comparative surplus of protein and phosphate in cow's milk as compared to breast milk. In the normal subject (including the baby) the usual diet produces an obligatory osmolar load of some 35–40 mOsm per 100 calories metabolized (i.e. per D.U. or per Kg. —in the first year of life), and water must be available to excrete these 40 mOsm, the water requirements for this purpose varying with age. The baby who is fully breast-fed produces a renal osmolar load of but 12 mOsm per D.U., which is hardly more than the 10 mOsm per

D.U. presented for renal excretion in the infant on an intravenous drip containing but glucose and water. When reasonable quantities of electrolyte are added to the drip, the osmolar load presented for excretion rises to about 20–25 mOsm per D.U.

As regards the *dilution* in which the osmolar content is to be excreted, infants (even premature infants) are as efficient as adults. They can both dilute urine to a level of about 100 mOsm (or even slightly less) of solute per litre of urine, i.e. if the circumstances warrant it an infant can produce something like 10 c.c. of water for each mOsm presented for excretion. To put it another way, if an individual is producing 40 mOsm of solute for excretion per D.U. (i.e. per Kg. in infancy, or per 3 Kg. in adulthood), then the maximum quantity of water which the body can supply for the excretion of such solute is about 400 c.c. per D.U. This is maximum dilution—from prematurity to senility. Further dilution cannot occur even though kidneys be maximally efficient, and when this figure is reached, any excessive quantities of body water still available must be kept within the body compartments—to result in tissue oedema and perhaps water intoxication.

By the 4th or 5th day of life a breast-fed infant is excreting (at maximal dilution) about 100 mOsm of solute per litre of urine (rather more solute in the first 3 days) and by this age he excretes about 100 c.c. urine daily, reaching 200 c.c. by the 10th day of life.

With regard to the ability to concentrate urine, infants have but poor function, if this be measured against adult abilities (though doubtless the function is more than adequate for the needs peculiar to infancy. It is wrong to call infantile function immature). An adult, if need be, can concentrate up to 1,400 mOsm of solute per litre of urine.[11] Thereafter there is a rapid increase in concentrating ability and somewhere between the first and second month of life virtually adult standards are attained. At this age their kidneys can concentrate up to 1,200 mOsm per litre of urine.[12]

In general the specific gravity of urine parallels the osmolar content (Table 1):[7]

TABLE 1

Sp.gr.	100.6	101.2	101.8	102.4	103.0	103.6
mOsm per Litre	200	400	600	800	1,000	1,200

This is really a rough approximation, and though there is generally a reasonably close corollation, this depends, in fact, on the type of solute excreted, as is indicated in Fig. 3. It is evident that acid salts (with the exception of NH_4Cl) have much lower osmolarity: Sp.Gr. ratios and would inevitably tend to lower the total osmolarity. If, as commonly happens in chronic renal insufficiency, the chief urinary solutes are the chlorides of Na, K and NH_4, then it will be clear that the Sp.G. will be low, in the region of 1.010.

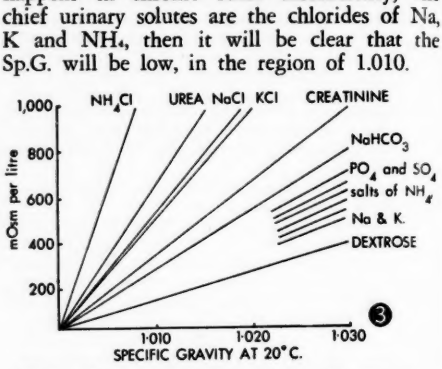

Fig. 3. Urine Osmolarity and Specific Gravity. (*From* Isaacson, L. C. (1959) *Lancet*, **1**, 72.)

The total osmolar load presented for kidney excretion can be gauged by means of estimating the plasma osmolar content. Fig. 2 illustrates the total mEq. values and also the total mOsm values for those ions—the large majority—with valencies of 1. The plasma values of Na, K, Cl and CO_2 give one an accurate guide to the total osmolar content. With a knowledge of these in terms of mOsm per litre one need add an estimated:

2 mOsm for protein $\left\{\frac{\text{16 mEq.}}{\text{8 valency}}\right\}$

\+ 2·5 mOsm for calcium (valency 2).

\+ 2 mOsm for various other constituents (Mg, Cu).

\+ ±8 mOsm for various inorganic and organic acids.

\+ 10 mOsm (5 each for urea and glucose).

The total unknown and estimated ionic content (in normal states) would then be about 25 mOsm, while the total (normal) known ion (Na 140–145; Cl 100–105; K5; bicarbonate 25–30) would be some 270–285 mOsm, the grand total being 25 + (270–285) = 295–310 mOsm per litre. An easier though less accurate method of gauging the osmotic panorama is by means of the formula (Na X 2) + 25 though with modern laboratory facilities it would be quite as easy and more accurate to use the formula $Na + Cl + K + CO_2 + 25$. An average normal plasma therefore has some 300 mOsm of solute per litre. It is unnecessary to indulge in the hair-splitting of referring to the solute in terms of per litre of plasma or per litre of plasma water.

Not only are the electrolytes within the plasma (and hence in its reservoir the interstitial fluid) of variable concentration but the

total plasma (and interstitial fluid) volume also varies with dehydration and overhydration. When there are two such variables, each may be expressed as a function of the other. Thus 300 mOsm per litre of plasma may be turned around, as it were, and the plasma water expressed in terms of mOsm. In this situation there would be some $\frac{1,000}{300}$ = 3.3 c.c. of plasma water per mOsm. This is a useful concept. Assuming that the total mOsm load is 250 mOsm per litre of plasma, we may imagine that the hypotonia consists of too little electrolyte per unit of fluid. But, on the other hand, it may be that the absolute total body electrolyte is, in fact, normal, but that overhydration is present. (In such a case serial weighings can resolve a dilemma). In this hypothetical example there will be 4 c.c. of plasma water per mOsm, and this is a pathologically high water ratio. In everyday clinical practice it is not usual—and indeed not necessary—to consider the 25 mOsm estimated to be present aside from the 4 commonly tested. These four alone (Na, K, Cl, CO_2) normally total some 270–285 mOsm per litre and a rough estimation of their osmolar concentration may be gauged from the formula: Na X 2. By turning these values 'upside down' we calculate that the normal range of plasma water: mOsm varies from $\frac{1,000}{285}$ to $\frac{1,000}{270}$, i.e. 3.5–3.7 c.c. per mOsm of solute.

We have already noted that an individual may require varying amounts of water to excrete fixed quantities of solute, and that whereas both infants and adults can dilute urine highly—with about 10 c.c. water per mOsm excreted, their concentrating ability varies. Adults can excrete 1 mOsm in about 1 c.c. (or even somewhat less) of water; very young infants need about 2 c.c. water per mOsm of solute. Thus in older children and adults maximum diluting and concentrating abilities vary from 10 c.c. to 1 c.c. water per mOsm of solute.

BODY LOSSES

Normally the secretions of the body are much in excess of the excretions. In adults and older children daily secretions from saliva, gut, bile, pancreatic and intestinal juice total more than twice the plasma volume (which is 5% of the body weight; or, to put it another way, 50 c.c. per Kg. or 25 c.c. per lb.). Hence one can appreciate the massive losses of fluid which may occur, e.g. from intestinal fistulae or severe diarrhoea.

The normal excretion of fluid takes place via the urine, the bowel, the lungs and the skin and oral intake makes good these losses. Daily fluid losses are roughly as follows (Table 2).

Thus the fluid requirements to replenish this loss are of the order of 150 c.c. per 100 calories metabolized.

Urine volume though listed as 80 c.c. per D.U., really varies immensely, depending on the amount of water available (1–10 c.c. per mOsm of solute) for excretion. However, there is a constant relationship at all ages between osmolar load, urine osmolar concentration and urine volume, viz.:

$$\text{Urine Volume in Litres} = \frac{\text{mOsmolar Load/Darrow Unit}}{\text{mOsmolar Concentration of Solute per Litre}}$$

Assuming a normal diet with an osmolar load of 40 mOsm per D.U. and a urinary solute load of (say) 400 mOsm per litre, then the urine volume is predictable. If, because of water lack, the urinary solutes are to be excreted at a concentration of (say) 1,200 mOsm per litre, then the urinary volume will again be predictable. Conversely, with a measured daily urine volume on a normal diet and without unusual extra-renal water losses, the urinary solute concentration can also be roughly predicted, viz.:

$$\text{mOsmolar Concentration of Solute per Litre of Urine} = \frac{\text{mOsmolor Load per D.U.}}{\text{Urine Volume in Litres}}$$

For example, an adolescent of 60 Kg. (20 D.U.) passing 1 litre of urine and having a normal diet, is likely to have

$$\text{mOsm per Litre} = \frac{40 \times 20}{1} = 800 \text{ mOsm of Solute per Litre of Urine.}$$

Stool water loss is but little, as is also the electrolyte loss within the stool. Normally some 2–3 mEq. (or mM.) each of Na, K, and

TABLE 2

Urine	80	c.c. per Darrow Unit: i.e. per Kg. in infants, or per 1·2 Kg. during nursery school years, or per 1·5 Kg. during primary school years, or per 2·0 Kg. at 10 years, or per 2·5 Kg. at puberty, or per 3·0 Kg. at adolescence and in adults.
Stool	8	
Lungs	14	
Insensible perspiration	28	
Mild sweating	20	
Total	150	

Cl per D.U. are excreted in the stool, but in the presence of diarrhoea stool water and electrolyte loss may increase greatly. In severe diarrhoea more than 15% of the body water (i.e. about 10% of the body weight) has been lost, and the average deficits of Na, K and Cl are of the order of 10 mM. each per Kg. body weight. A diarrhoeal stool often has in the region of 60 mM. of Na and of K per litre (or per Kg.) of stool and about 40 mM. per litre of chloride. Thus diarrhoeal stools, in general, have hypotonic concentrations (as compared to plasma) of electrolytes, though in the bacterial dysenteries rather more electrolyte tends to be lost.

Insensible perspiration is in the region of 30 c.c. per D.U., and occasionally perhaps more. Sweat loss rises rapidly with increasing environmental and body temperature. For each 1° C. elevation in body temperature sweat loss increases by 3 c.c. per Kg. Whereas a minor sweat loss may be in the order of 20 c.c. per D.U., this value may reach 50–70 c.c. per D.U. and in very hot humid atmospheres there may be losses of 100 c.c. per D.U.[13]

In normal subjects sweat contains little electrolyte, the Na varying from 10–30 mM. per litre, K 3–10 mM. per litre and Cl 10–35 mM. per litre. Infant sweat has less electrolyte, the Na being some 5 mEq. per litre and K 6 mEq. per litre, a Na:K ratio of less than 1. Older children have levels which more closely approximate the adult Na:K ratio of 4:1.[13]

The total insensible loss (lungs 14 c.c., skin 28 c.c.) is about 42 c.c. or g. per 100 calories metabolized in the absence of sweat. This totals to something like 1/4 or 1/3 of all fluid loss. Lung water loss may easily rise 3- or 4-fold with hyperventilation, and if there be mild sweating as well, then something like 50% of fluid lost from the body may be disposed of by virtually insensible and unappreciated means, so that though insensible loss be very considerable, it is easily overlooked, for what the eyes see not, the fluid balance chart does not take into account.

In older children and adults daily fluid loss from the lungs is of the order of 400 c.c. per day and easily 800 c.c. from insensible perspiration.

(To be concluded)

NOTES AND NEWS : BERIGTE

BOOTS APPOINTMENT DIARY FOR 1961

Copies of this diary are available for distribution to medical practitioners. Those interested should write without delay to: B.P.D. (S.A.) (Pty.) Ltd., P.O. Box 45, Jeppestown, Transvaal.

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UNIVERSITY OF CAPE TOWN

REFRESHER COURSE FOR GENERAL PRACTITIONERS

23–27 JANUARY 1961

A Refresher Course for General Practitioners will be held, consisting of lectures, ward rounds and demonstrations in Medicine, Surgery, Obstetrics and Gynaecology and the Specialities at appointed times between 8 a.m. and 5.30 p.m. daily from 23 to 27 January. Practitioners who wish to spend a further three days to attend special clinics, departments, operations, etc. are welcome to do so but, unfortunately, will not be able to remain in Medical Residence for this extended period as the students will have returned.

The Course will probably include the following:

A. *Ward rounds* with senior members of the teaching staff in Medicine, Surgery, Dermatology, Paediatrics, Obstetrics and Gynaecology.

B. *Panel discussions* by groups of consultants on a variety of subjects including the following:

Everyday surgical procedures.
Common surgical lesions in infants and children.
Assessment and Management of Hypertension.
Hormones in practice.
Acute Trauma—Head, Abdominal and Thoracic.
Common Obstetrical and Gynaecological Problems.
Psychological Problems in Practice (including Alcoholism).

A feature of these discussions is that ample opportunity will be provided for members of the panel to answer questions raised by the practitioners attending the Course.

C. *Demonstrations* by the Consultant staff of the following:

Anaesthetic Techniques and Minor Surgery.
Minor Gynaecological Procedures.
Everyday Orthopaedic Methods.

D. *A Lecture-Demonstration* on the following subjects:

Recent work on Haemoglobin Levels in Childhood.
Common Skin Diseases.

E. Sessions *Any Questions.*

Special sessions will be provided in General Surgery, Medicine, Ophthalmology and Otorhinolaryngology, Paediatrics and Gynaecology and Obstetrics at which a panel of members will answer questions asked by General Practitioners on any subject not covered by the programme of the Course.

The number of practitioners who can be accepted for the Course is restricted.

The fee for the Course will be 5 guineas, payable in advance to the Registrar, University of Cape Town. This fee should not be sent until the applicant has been notified that he will be admitted to the Course.

Board and lodging will be available at Medical Residence for those desiring it (and for their wives) at a charge of one guinea per day per person.

Applications for admission to the Course, stating whether residential accommodation will be required or not, should be submitted as soon as possible to the Registrar, University of Cape Town, Private Bag, Rondebosch.